

## Meeting Report

**Neuro-  
degenerative  
Diseases**

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# 6th Fabisch Symposium for Cancer Research and Molecular Cell Biology – Enzymes in Physiology and Pathogenesis: Signaling by Secretases

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The molecular basis of Alzheimer disease still holds many unsolved secrets. To face those scientific issues, scientists from over 10 different countries met at an Alzheimer disease conference in Berlin on September 24–26, 2009. The venue selected by the organizers Lisa Munter and Gerd Multhaup was the brand-new conference hotel ‘Seminaris’ opened in 2009 on the campus of the Free University Berlin (FU Berlin). This campus stands out by its unique historical ambiance as at the beginning of the 20th century numerous Nobel laureates worked there. It was the 6th meeting in a row funded by the Luzie Fabisch Foundation (box 1). During the meeting, young scientists were given plenty of opportunities to discuss topics with leading and highly recognized researchers of the field, which was reflected by the size of the meeting, with a neat number of approximately 60 participants including 24 speakers. Medical and biochemical topics on signaling in Alzheimer and cancer research were combined and addressed precisely the cutting-edge-of-science issues of Alzheimer disease. Intensive discussions dealt with the mechanisms affecting processing pathways of key molecules involved in the pathogenesis of Alzheimer disease, such as  $\beta$ -amyloid ( $A\beta$ ) peptides, amyloid precursor protein (APP), tau protein and the secretases (fig. 1).

As part of the social program, Jens-Peter Fürste from the FU Berlin provided an enjoyable overview on the scientific history of Berlin-Dahlem. Beyond doubt, the historical walk led by Fürste through the FU campus, passing the villa of Fritz Haber and the impressive buildings of the former Kaiser Wilhelm Society, which are now owned by

the Max Planck Society or the FU Berlin, was a highlight. The tour showed where the tremendous work by Max Delbrück, Otto Warburg, Lise Meitner, Otto Hahn, Fritz Strassmann and Gerhard Ertl was done, just to mention a few.

The scientific part of the meeting was opened by John Hardy from the University College, London, UK, delineating the future developments of genetic analysis in the understanding of Alzheimer disease. Besides the analysis of loci contributing to the risk of sporadic diseases, genome-wide association studies will direct towards distinct genetic variability linked with diseases. Switching to the protein level, Peter St. George-Hyslop from the University of Toronto, Canada, reported on the enzymatic steps generating  $A\beta$  peptides, the major pathogenic agent leading to Alzheimer disease. The main enzyme, named  $\gamma$ -secretase, shows only enzymatic activity when assembled in a complex arrangement of several proteins requiring specific interaction motifs, i.e. histidine residues in certain transmembrane sequences of one subunit. Functional protein networks assembled by interaction motifs are also central to the research interests of Gerd Multhaup from the FU Berlin, Germany. Key molecules like APP and BACE1 ( $\beta$ -site APP-cleaving enzyme), which are involved in the molecular mechanisms of Alzheimer disease, form dimers and represent risk factors for toxic  $A\beta$  formation in their oligomerized forms. In addition, he presented evidence that  $A\beta$  peptides may have a role in nuclear signaling.

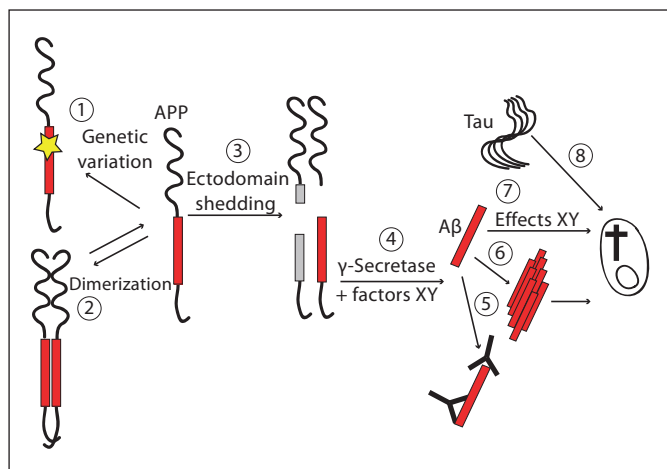
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**Fig. 1.** Schematic overview of the topics presented at the meeting. Processing of APP and A $\beta$  generation were main themes; in particular, genetic variations (No. 1, star) leading to or preventing Alzheimer disease were discussed (John Hardy, Nir Barzilai, Claudio Franceschi, Michele Mishto). Multiple effects of APP and protein oligomerization were reported (No. 2; Gerd Multhaup, Daniela Kaden, Michael Schaefer). APP processing is initiated by ectodomain shedding (No. 3) by BACE1 or ADAM10, where the latter prevents generation of A $\beta$  indicated in gray (Alistair Garratt, Paul Saftig, Otmar Huber). Further cleavage of the A $\beta$ -containing C-terminal stub of APP by  $\gamma$ -secretase generates A $\beta$  peptides, a step that is influenced by additional factors (No. 4; Peter St. George-Hyslop, Patrick Fraering, Amantha Thathiah). Vaccination strategies can prevent A $\beta$  toxicity (No. 5; Christoph Hock). A $\beta$  aggregation causes cytotoxicity (No. 6, illustrated by the cross inside the cell; Charles Duyckaerts, Lin Hung, Thomas Bayer, Lars Lannfelt). A $\beta$  peptides might also lead to cell death by other effects (No. 7; Jacques Hugon, Jörg Tatzelt, Dietmar Schmitz), and also aggregates of the tau protein add to cytotoxicity (No. 8; Luc Bueé, Ilse Dewachter, Christian Haass).

APP is a membrane-residing protein with functions which are still not well understood. Contributing to the solution of this enigma, Daniela Kaden from the FU Berlin, Germany, reported on the impact of metal ions on the localization and formation of cell-cell contacts by APP and its homologous proteins. The first enzyme in the generation of Alzheimer-disease-associated A $\beta$  peptides is the  $\beta$ -secretase BACE1, which sheds the ectodomain of APP. Alistair Garratt from the Max Delbrück Center for Molecular Medicine in Berlin, Germany, focused on signaling events commenced by BACE1 cleavage of neuregulin 1, thereby investigating *in vivo* functions of BACE1 besides the generation of toxic A $\beta$  molecules. APP shedding can also be protective when the members of the ADAM (a disintegrin and metalloproteinase) family of

proteases are active. The presentation by Paul Saftig, Christian Albrecht University, Kiel, Germany, provided insights into the *in vivo* function of ADAM10 for APP processing in the brain. As he says: 'The regulation of these proteases is complex and still poorly understood. Studies in classical and conditional ADAM knockout mice revealed their partially redundant roles in angiogenesis, neurogenesis, tissue development and cancer.'

After APP has undergone ectodomain shedding, the  $\gamma$ -secretase complex is the final enzyme to produce A $\beta$ . Particularly, Patrick Fraering from the Brain Mind Institute, EPFL Lausanne, Switzerland, specified  $\gamma$ -secretase as 'an emerging therapeutic target for several types of cancer and for Alzheimer disease. To predict cross-reactions and run risk assessments for  $\gamma$ -secretase-targeting clinical trials, we identified genes and molecular functions transcriptionally susceptible to  $\gamma$ -secretase activity changes'. Amantha Thathiah from the Catholic University of Leuven, Belgium, reported on a successful high-throughput functional genomic screen, which identified the G-protein-coupled receptor 3 as a novel modulator of  $\gamma$ -secretase localization and thereby of A $\beta$  generation.

The toxicity of A $\beta$  peptides might be explained by several independent pathways. Jacques Hugon from the University Paris 7, France, found that the A $\beta$  peptide might also be involved in translational control. Furthermore, Lin Hung from the University of Melbourne, Australia, provided evidence that especially dimerized A $\beta$  peptides interact with lipid surfaces and might thereby cause cytotoxicity. Lars Lannfelt from Uppsala University, Sweden, described soluble A $\beta$  aggregates as bioactive species by using a novel protofibril selective antibody and a mouse model carrying the hereditary Arctic mutation in the A $\beta$  sequence as well as patient-derived brain material. Another A $\beta$  modification was presented by Thomas Bayer from the Georg August University, Göttingen, Germany. Based on novel observations from Alzheimer disease patients' brains, he developed mouse models generating N-terminal-truncated and pyroglutamate-modified forms of A $\beta$  and found especially those peptides to cause neurodegeneration and concomitant neurological deficits.

Switching from the laboratory approaches to the clinical level, Christoph Hock from the University of Zürich, Switzerland, gave an update on recent developments in immunotherapy against A $\beta$ . He says: 'Antibodies against A $\beta$  are able to cross the blood-brain barrier and mediate clearance from brain by microglia cells. Such intervention should be initiated early in the course of Alzheimer disease, ideally prior to the onset of clinical signs of dementia.' He pointed out that the brain's blood flow has a

major role in A $\beta$  clearance and would deserve more attention in early stages of Alzheimer disease.

Besides these exciting progressions in the amyloid research field, other proteins involved in aging and Alzheimer disease were intensively discussed. Regarding the tau protein, Charles Duyckaerts from the Hôpital de la Salpêtrière, Paris, France, Luc Buée from the University of Lille, France, and Ilse Dewachter from the Catholic University of Leuven, Belgium, reported on the impact of tau phosphorylation in normal aging, the cognitive decline caused by abnormal tau protein and its relation to amyloid pathology. Christian Haass from the Ludwig Maximilian University and the 'Deutsches Zentrum für Neurodegenerative Erkrankungen' in Munich, Germany, presented a novel tau model. It is 'a tau-transgenic fluorescent zebrafish, which displayed a number of the cardinal features of tauopathies. These included abnormal phosphorylation and folding of tau, tangle formation, a movement phenotype and neuronal cell death. For the first time in the field, we were able to monitor cell death by in vivo imaging.' Using this model organism, he also found that methylene blue, a drug which was shown to slow memory decline in human patients, failed to rescue any of the tau-dependent phenotypes. Further, to learn from other diseases dealing with aberrant aggregation of proteins, Jörg Tatzelt from the Ludwig Maximilian University and the 'Deutsches Zentrum für Neurodegenerative Erkrankungen' in Munich, Germany, presented an interesting link between the prion protein and A $\beta$ : 'In prion diseases affecting humans and animals, the cellular prion protein (PrP<sup>C</sup>) is converted into a neurotoxic conformer designated as PrP<sup>Sc</sup>. We have previously demonstrated that PrP<sup>Sc</sup> misuses PrP<sup>C</sup>-dependent signaling pathways for neurotoxic signaling. We now present evidence that toxic signaling of soluble oligomers of A $\beta$ , secreted by transfected cells or prepared from chemical synthesis, is also dependent on the expression of physiological active PrP<sup>C</sup>.' He also showed that dimerization of PrP<sup>C</sup> increases the resistance of cells to stress conditions.

These contributions on key players in the field of neurodegenerative disorders were complemented by important presentations from closely related research fields such as cellular signaling of the cadherin/catenin system presented by Otmar Huber, Friedrich Schiller University, Jena, Germany, or mechanisms of ion channel assembly reported by Michael Schaefer from the University of Leipzig, Germany. In the fields of electrophysiology and neurotransmission, Dietmar Schmitz from the Charité Berlin, Germany, highlighted the importance of the molecular processes at glutamatergic synapses.

Finally, a session about novel observations derived from genetic centenarian trials convinced the auditorium that learning from the healthy oldest old might help to understand age-related diseases. Nir Barzilai from the Einstein College of Medicine in New York, USA, discussed novel mechanisms protecting against age-related decline in cognitive function, Claudio Franceschi from the University of Bologna, Italy, presented studies with mitochondrial DNA from their centenarian cohorts, and Michele Mishto, Charité Berlin, Germany, discussed the meaning of the immunoproteasome in neurodegenerative diseases.

Finally, besides the Luzie Fabisch Foundation the organizers are grateful to the Verum Foundation (box 2), the GRK 1123 and Bruker Daltonics for financial support. For more information see <http://tinyurl.com/AlzheimerFabisch>.

### Box 1

#### *Who Was Luzie Fabisch?*

Luzie Fabisch donated to the Freie Universität Berlin a sizeable sum of money and dedicated it to 'Cancer Research and Cellular Biology'. To give the donation maximum impact, the university decided to set it aside for young, not yet settled researchers of the Department of Biology, Chemistry and Pharmacy, who wish to organize a symposium related to their field of research. The leverage of the interest originating from the Luzie Fabisch Fund is considerable: in a series of topical symposia, young promising members of the department took advantage by constituting, without major bureaucratic impediments, a forum for colleagues working in their respective fields, a meeting point for exchange and discussion of data and ideas, simultaneously making themselves known as new and active members of their community.

*Ferdinand Hucho*, honorary chairman of the Luzie Fabisch Foundation

### Box 2

All participants were asked to vote on the best poster presented. Poster prizes were funded by the Verum Foundation and were awarded to:

- (1) Zoë Goodger, ETH Zürich, Switzerland – 'β-Cleavage of APP in endosomes leads to A $\beta$  production and nuclear signaling by AICD',
- (2) Mohiuddin Quadir, FU Berlin, Germany – 'Dendritic polyglycerol as drug delivery platform for Alzheimer disease',
- (3) Janos Steffen, Annett Koch, Elke Krüger, Charité Berlin, Germany – 'The transcription factor TCF11 induces de novo formation of proteasomes to compensate for inhibition of proteasome activity', and
- (4) Heinke Schieb, University of Duisburg-Essen, Germany – 'Profiling of membrane-anchored β-secretase inhibitors in cell cultures'.